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5- α -Reductase deficiency causing male pseudohermaphroditism

Growth of the phallus, fusion of the labia, and formation of the scrotum in males require the conversion of testosterone to 5- α -dihydrotestosterone (DHT) at tissue level. The enzyme required for this conversion is 5- α -reductase which is found in high concentration in fetal urogenital tissue (Wilson, 1975). Testosterone itself brings about obliteration of the lower part of the vagina and descent of the testis. Lack of 5- α -reductase produces a form of fetal

androgen insensitivity which has specific clinical features (Peterson *et al.*, 1977). Recognition of the condition is crucial to deciding on the sex of rearing.

Case history

The baby was born at term by normal delivery in Lahore, West Pakistan. Birthweight was 3.5 kg. The pregnancy was uneventful and no drugs were ingested. The parents were unrelated and there was no relevant family history.

Ambiguous genitalia were noted at birth. At age 2½ years the patient was brought to the UK for investigation. Physical development and milestones were normal. Length was on the 50th centile. Examination of the external genitalia (Figure) revealed two palpable testes in labial folds and a slightly enlarged clitoris with an urethral opening at its base. There was no vaginal opening.

Investigations showed normal male karyotype. Diurnal values of plasma cortisol and ACTH were normal. After 3 injections of human chorionic gonadotrophin 750 units on alternate days, plasma testosterone rose from 0.8 to 15.8 and 17.8 nmol/l (0.2 to 4.6 and 5.2 ng/ml) on days 4 and 6. Testicular biopsies showed seminiferous



Fig. Age 2½ years, ambiguous external genitalia.

tubules containing both sertoli cells and spermatogonia. Leydig cells were also present in both testes.

5- α -Reductase activity was estimated in scrotal skin according to the method of Wilson and Walker (1969). 82 mg scrotal skin were incubated as 0.5 mm slices in Krebs-Ringer bicarbonate buffer with glucose and 1, 2, 6, 7 ^3H testosterone at a concentration of 10^{-8} mol/l for 60 minutes at 37°C. The medium and tissue were extracted twice with ethyl acetate. 30 μg each of testosterone and 5- α -dihydrotestosterone were added to the dried extract and the mixture was applied to a paper chromatogram and run in a descending direction for 16 hours in a Bush A system.

Testosterone was located by viewing under ultra-violet light and 5- α -dihydrotestosterone by comparison with standard strips stained with Zimmermann reagent. The chromatogram was examined by a strip scanner and two radioactive peaks were found, one corresponding to testosterone and one running in front of where DHT would be expected. This second peak and the DHT area were eluted with ethanol and examined by gas-liquid chromatography using an electron capture detector. DHT was found only where it would have been expected and not associated with the second radioactive peak, which was probably 4 Δ -androstenedione. The eluate was also assayed in a liquid scintillation counter and again activity could not be detected in the DHT area. The conclusion was that there was absence of 5- α -reductase activity in the scrotal skin.

The infant subsequently underwent a first-stage repair of his perineal hypospadias with correction of chordee and removal of prepubic fat to improve the appearance of the phallus. Examination under anaesthetic confirmed absence of muellerian structures.

At the end of these investigations the child was joined by his mother who brought with her a newly-born male sibling whose genitalia were identical in appearance with those of the index patient. No investigations have yet been carried out on this sibling.

Discussion

The development of the bipotential fetal gonad at the 6th week of organogenesis is dependent on the sex chromosomes present. A Y-chromosome, even in an aberrant form, is associated with the presence of H-Y antigen which ensures differentiation of a testis. The subsequent development of the Wolffian system is dependent on testosterone secreted by the testis; development of the external genitalia requires conversion of testosterone to 5- α -dihydrotestosterone at tissue level (Wilson, 1975).

Two male negro siblings with ambiguous genitalia, initially classified as having 'pseudovaginal perineo-scrotal hypospadias', were found to have an inability to convert testosterone to dihydrotestosterone and were reported from Texas (Walsh *et al.*, 1974). 38 male pseudohermaphrodites from 24 families have been discovered in 4 villages in the south-western section of the Dominican Republic, demonstrating a similar defect (Peterson *et al.*, 1977). This case is the first reported as originating from Asia and, like the other cases, the 5- α -reductase deficiency is presumed to be inherited as an autosomal recessive (male limited) because our patient has a younger sibling with identical genitalia. It could, alternatively, be inherited as an X-linked recessive condition.

This diagnosis is important to make because it affects the decision on the sex of rearing. 5- α -Reductase activity in sex-sensitive skin rises during the 3 months after birth in normal subjects and then falls progressively, reaching levels in adults which are as low as those observed in nonperineal skins from subjects of all ages (Wilson and Walker, 1969). The events of male puberty, growth of the penis and sex hair, are dependent on testosterone itself. Thus patients with 5- α -reductase deficiency, in contradistinction to patients with the various forms of androgen insensitivity (testicular feminisation), masculinise at puberty. The voice deepens, there is no breast development, and the phallus enlarges to become a functional penis. The change is so striking that in Salinas, in the Dominican Republic, the patients are called *guevedoces*-penis at 12 years of age (Imperato-McGinley *et al.*, 1974). Whether dihydrotestosterone is important for growth of the internal male organs at puberty is not known, but 5- α -reduced androgens may play a part in the differentiation and maturation of sperm (Wilson, 1975).

In our patient we attempted to correct the hypospadias early and strongly recommended rearing as a boy for the reasons given. It would be extremely unfortunate if such cases were regarded as girls in the expectation of female characteristics developing at puberty, as happened in the first discussed cases. It would be equally wrong to treat such cases as if they had the micropenis syndrome and to consider converting the sex of rearing to a female one (Grant *et al.*, 1976). Psychosexual orientation in pubertal patients is male, and spermatogenesis has been demonstrated in a testicular biopsy of an affected subject (Peterson *et al.*, 1977). It is not known whether the patients are fertile.

Summary

An infant with male pseudohermaphroditism due to

deficiency of 5- α -reductase is described, the elder of two affected male siblings. These patients, who come from Pakistan, are the first to be described outside America.

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Congenital dyserythropoietic anaemia type I in two brothers presenting with neonatal jaundice

Congenital dyserythropoietic anaemia (CDA) is a name given to a group of hereditary refractory anaemias which show ineffective erythropoiesis, characteristic morphological abnormalities of the erythroblasts, an inappropriately low reticulocyte response, mild hyperbilirubinaemia, splenomegaly, and secondary haemochromatosis. From their morphological and serological features these anaemias have been classified into 3 groups although there is some overlap between them (Heimpel and Wendt, 1968). Type I is characterised by macrocytosis and internuclear chromatin bridges, type II shows

binucleated and multinucleated normoblasts and positive acidified serum lysis, and type III has giant multinucleated erythroblasts. CDA type I, first described by Heimpel *et al.*, in 1968, appears to be the least common of this rare group of anaemias with 21 cases reported—including three pairs of siblings (Heimpel, 1976). This report describes 2 brothers with CDA type I, both of whom presented with neonatal jaundice.

Case reports

Case 1. A 3.5 kg baby boy was admitted to this hospital at 2 days following vacuum extraction at 38 weeks after spontaneous onset of labour. The liquor was noted to be deep orange. Apgar scores were 4 at 1 minute and 9 at 10 minutes. Cord blood serum bilirubin was 60 $\mu\text{mol/l}$ (3.5 mg/100 ml) and the direct antiglobulin test was negative. Before being transferred to this hospital a cyanotic episode had occurred, slight jaundice was clinically evident, and treatment with antibiotics was begun because of suspected neonatal sepsis. The patient was the first child of unrelated parents and there was no family history of any haematological disorder. Examination revealed a slightly jaundiced, term infant with 2 cm hepatomegaly and 3 cm splenomegaly. Blood count showed Hb 14.5 g/dl, WCC $25.0 \times 10^9/\text{l}$; 25 000/ mm^3 (neutrophils $15.5 \times 10^9/\text{l}$, lymphocytes $8.0 \times 10^9/\text{l}$; 15 500/ mm^3 , 8000/ mm^3), nucleated RBC $5.4 \times 10^9/\text{l}$ (5400/ mm^3), and platelet count $50 \times 10^9/\text{l}$ (50 000/ mm^3). Red cells showed anisopoikilocytosis, macrocytosis, fragmented cells, and a few stipple cells. Serum bilirubin was 67 $\mu\text{mol/l}$ (3.9 mg/100 ml). Direct antiglobulin test was negative and blood groups of both mother and baby were A-positive. Bacterial cultures and search for prenatal infective agents were negative and antibiotics were stopped on the 7th day. When discharged at 19 days he was well with 1 cm hepatosplenomegaly, Hb 10.5 g/dl, WCC $15.0 \times 10^9/\text{l}$ (15 000/ mm^3) platelets $400 \times 10^9/\text{l}$ (400 000/ mm^3), and the nucleated red blood cells had disappeared. At 8 weeks he was readmitted with Hb 6.3 g/dl and transfused with packed red cells. The abnormal red cell morphology was unchanged and the provisional diagnosis was infantile pyknocytosis.

During the subsequent 2 years he remained well but had persistent hepatosplenomegaly of 1 cm. Hb varied between 8.5 and 10.5 g/dl, reticulocytes between 1.0 and 2.5%, serum bilirubin was 19 $\mu\text{mol/l}$ (1.1 mg/100 ml), and haptoglobins were absent. The blood film showed persistent abnormal red cell morphology characterised by anisopoikilocytosis, macrocytosis, fragmented cells, and stipple cells. Blood counts and red cell morphology of both